

Involvement of microsatellite instability in colorectal cancer – review

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Abstract. Background. Microsatellites, also known as Short Tandem Repeats (STRs) are short (1-6 base pairs) repeating segments of DNA scattered throughout the human genome, accounting for approximately 3% of it. Microsatellite instability occurs in about 15% of gastrointestinal cancers, being associated with specific clinical, pathologic and molecular features of the tumors. **Genetic mechanism, clinical features and treatment influence.** Microsatellite instability (MSI) in colorectal cancers occurs through different mechanisms. MSI in sporadic colorectal cancer usually appears because of epigenetic silencing of the DNA mismatch repair gene MLH1, being associated with methylation. Regarding hereditary non-polyposis colorectal cancer (HNPPC), all the cases present microsatellites that had changed in length, not only in the critical genetic region but virtually everywhere in the genome of the tumor. The common presence of microsatellite instability in HNPPC is related to the defective DNA mismatch repair proteins determined by germline mutation of one of the three main genes (MLH1, MSH2 and MSH6). In contrast to patients with chromosomal instability pathway (CIN), who present mutations in p53 and APC genes, including major chromosomal abnormalities, the patients who present MSI have mutations in specific genes, such as transforming growth factor beta receptor II (TGF- β RII) and beta-catenin, with fewer mutations being found in p53 and K-ras genes. Also, there have been a number of studies regarding the response of patients diagnosed with colorectal cancer and microsatellite instability to various chemotherapy protocols. **Conclusion.** Understanding the genetic mechanisms of tumor development in patients with colorectal cancer involving the aspect of the microsatellite instability pathway has an important role in the diagnosis and prognosis of these patients, as well as a personalized surgical and chemotherapy treatment, with better oncological results.

Keywords: microsatellite, instability, colorectal, cancer.

Background

Microsatellites, also known as Short Tandem Repeats (STRs) are short (1-6 base pairs) repeating segments of DNA scattered throughout the human genome, accounting for approximately 3% of it. Because of their repeated structure, microsatellites have a predisposition for high mutation rates. Microsatellite instability is a molecular phenotype determined by a defective DNA mismatch repair system (1–3).

Microsatellite instability occurs in about 15% of gastrointestinal cancers, being associated with specific clinical, pathologic and molecular features of the tumors (4). The presence of microsatellite instability was found in the sporadic colon, gastric and endometrial cancers, but was also determined in many other cancers,

such as ovarian cancer, sebaceous carcinoma, glioblastomas or lymphomas (5,6).

Colorectal cancer has been defined as a genetically heterogenous disease, with two main different pathways being identified in the

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sequence adenoma-carcinoma that is responsible for the development of colorectal cancer in most patients – the chromosomal instability pathway (CIN), the most prevalent molecular cause of genomic instability in colorectal cancer, accounting for approximately 65-70% of all sporadic colorectal tumors (7), and the microsatellite instability (MSI) pathway, responsible for 8-20% of all colorectal tumors (8–15).

Genetic mechanism

Microsatellite instability in colorectal cancers occurs through different mechanisms. MSI in sporadic colorectal cancer usually appears because of epigenetic silencing of the DNA mismatch repair gene MLH1, being associated with methylation. DNA methylation is associated with worse outcomes in colorectal cancer, but this negative prognostic influence does not appear in methylated tumors with MSI (16–18). Regarding hereditary non-polyposis colorectal cancer (HNPPC), all the cases present microsatellites that had changed in length, not only in the critical genetic region but virtually everywhere in the genome of the tumor (16). The common presence of MSI in HNPPC is related to the defective DNA mismatch repair proteins determined by germline mutation of one of the three main genes (MLH1, MSH2 and MSH6). In consequence, the lifetime risk of developing colorectal cancer is more than 80% in the children of patients with HNPPC, opposing a lifetime risk of colorectal cancer of up to 5-6% in the general population (19,20).

In contrast to patients with CIN, who present mutations in p53 and APC genes, including major chromosomal abnormalities, the patients who present MSI have mutations in specific genes, such as transforming growth factor beta receptor II (TGF- β RII) and beta-catenin, with fewer mutations being found in p53 and K-ras genes (21,22).

For testing the MSI, the specimen is represented by the surgically resected colorectal tumors and the surrounding normal tissue, whereas for the rectal tumors that undergo neoadjuvant therapy, the sample is better represented by the initial biopsy of the tumor (23). The procedure testing the MSI involves a polymerase chain reaction (PCR) amplification

of microsatellite repeats and comparing their size along with DNA in normal cells versus tumor cells (24,25). Based on a series of five nucleotide markers, MSI-H (high) is defined when at least two out of five markers in tumor cells show variability in size compared with normal cells, MSI-L (low) is defined when only one marker shows variability and MSS (microsatellite stable) is defined when there is no unstable marker in the DNA of tumor cells (24).

Clinical and pathological features

Differences were noted between the patients that were diagnosed with colorectal cancer and presented microsatellite instability opposite to patients that had chromosomal instability. MSI-H was observed more often in women and in proximal/left colonic cancer, whereas CIN was determined especially in patients with left/distal colon. Also, tumors presenting MSI are usually diploid, poorly differentiated, often mucinous and have lymphocyte infiltrate similar to Crohn's disease, while patients with CIN are usually aneuploid/polyploid, highly differentiated, rarely mucinous and in most cases have no lymphocytic infiltrate. Furthermore, MSI is associated with larger, T₃ tumors, but with a more favorable stage, having less node involvement and reduced cases of metastases (26–32).

Patients with colorectal cancer and MSI have longer survival periods than patients with CIN mutations and similar cancer stages (33,34). Also, patients that are diagnosed with hepatic metastases from colorectal cancer rarely present MSI (35). Mutations of p53 gene have been related to a poor prognosis (36), occurring less commonly in patients that exhibit MSI than in those that exhibit CIN. In addition, tumors with MSI that present a mutation of the p53 gene tend to be more aggressive than tumors with MSI and lack of the p53 gene mutation (26).

A series of studies have demonstrated a lower recurrence rate in patients with MSI tumors compared to patients with MSS tumors (37,38). Other studies have also shown a lower recurrence risk and a better prognosis in patients with colorectal cancer and MSI-H phenotype with II-stage tumors compared to patients diagnosed with colorectal cancer and MSI-L/MSS phenotype

(39–41). There was reported a reduced incidence rate of MSI-H tumors in stages III/IV than I/II stages, demonstrating a lesser possibility of metastases in these patients (42,43).

Chemotherapy influence

There have been a number of studies regarding the response of patients diagnosed with colorectal cancer and microsatellite instability to various chemotherapy protocols. Not only those researches have shown that there is no benefit from single-agent fluoropyrimidine therapy in MMR-deficient colorectal tumors (44–47) and resistance of MSI-H patients to treatment with 5-fluorouracil, but also that the patients that received chemotherapy with 5-fluorouracil had lower survival compared to patients that did not receive this treatment (47,48). Positive results were observed with oxaliplatin-based chemotherapy, with more disease-free survival (49) and there are some studies that suggest that MSI-H colorectal cancer cells are more sensitive to irinotecan compared to MSS colorectal cancer cells, with a complete response rate to neoadjuvant therapy with irinotecan being of 60% in case of MSI-H patients opposing 20% in case of MSS patients (50).

Conclusion

Understanding the genetic mechanisms of tumor development in patients with colorectal cancer involving the aspect of the microsatellite instability pathway has an important role in the diagnosis and prognosis of these patients, as well as personalized surgical and chemotherapy treatment, with better oncological results.

Conflicts of Interest: The authors declare no conflict of interest.

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